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(54) Title: TREATMENT OF ADULT RHEUMATOID ARTHRITIS BY ORAL ADMINISTRATION OF POOLED HUMAN IMMUNOGLOBULIN AND AN ANTACID

(57) **Abstract**

Pooled human immunoglobulin and an antacid may be administered orally to adult rheumatoid arthritis patients to treat the rheumatoid arthritic condition of those patients. Oral administration of pooled human immunoglobulin in conjunction with an antacid results in significant clinical improvement in the level of disease activity in patient with adult rheumatoid arthritis.

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TREATMENT OF ADULT RHEUMATOID ARTHRITIS BY ORAL ADMINISTRATION OF POOLED HUMAN IMMUNOGLOBULIN AND AN ANTACID

FIELD OF THE INVENTION

The present invention relates to the treatment of adult rheumatoid arthritis. More particularly, the invention relates to the treatment of adult rheumatoid arthritis by oral administration of a pharmaceutical composition comprising pooled human immunoglobulin in conjunction with an antacid.

BACKGROUND OF THE INVENTION

Adult rheumatoid arthritis is a systematic inflammatory disease that commonly affects the joints, particularly those of the hands and feet. The onset of rheumatoid arthritis can occur slowly, ranging from a few weeks to a few months, or the condition can surface rapidly in an acute manner.

Today, over 2,500,00 individuals are diagnosed with adult rheumatoid arthritis in the United States alone (1% of population), with some statistics indicating that from 6.5 to 8 million adults are potentially afflicted with the disease. Women are affected 2-3 times more often than men. Adult rheumatoid arthritis can

occur in young adults and typically will increase in incidence with age.

The classic early symptoms of adult rheumatoid arthritis include stiffness, tenderness, fever, subcutaneous nodules, achy joints, and fatigue. The joints of the hands, feet, knees and wrists are most commonly affected, with eventual involvement of the hips, elbows and shoulders. As the joints stiffen and swell, any type of motion becomes very painful and difficult. The more severe cases of adult rheumatoid arthritis can lead to intense pain and eventual joint destruction. Some 300,000 bone and joint replacement surgical procedures are performed annually in an effort to alleviate the pain and mobility loss resultant from arthritis related joint destruction.

Adult rheumatoid arthritis and juvenile rheumatoid arthritis are two different diseases. Juvenile rheumatoid arthritis is most common in children and includes eight different forms of disease. One form of juvenile rheumatoid arthritis, Rf-positive polyarticular juvenile rheumatoid arthritis, bears some resemblance to adult rheumatoid arthritis. However, only about 40% of all juvenile rheumatoid arthritis cases are polyarticular and, of these, only about 5-10% are rheumatoid factor (Rf) positive. Therefore, only 2-4% of juvenile rheumatoid arthritis patients suffer from Rf-positive polyarticular juvenile rheumatoid arthritis.

Juvenile rheumatoid arthritis is characterized by abnormal T and B cell function and selective IgA deficiency. Adult rheumatoid arthritis is a disease identified by the presence of auto-antibodies including certain characteristic rheumatoid factors. The

immunogenetic associations, clinical course, and functional outcome of juvenile rheumatoid arthritis are quite different from adult-onset rheumatoid arthritis. Pediatric Rheumatic Diseases In: Primer on the Rheumatic Diseases, 11ed. 1997 (incorporated herein by reference).

The effective treatment of adult rheumatoid arthritis has generally employed a combination of medication, exercise, rest and proper joint protection therapy. The therapy for a particular patient depends on the severity of the disease and the joints that are involved. Aspirin is widely used for pain and to reduce inflammation. In addition to aspirin, non-steroidal anti-inflammatory drugs, corticosteroids, gold salts, anti-malarials and systemic immuno-suppressants are widely used in moderate to advanced cases. The use of steroids and immunosuppressants, however, has significant risks and side effects both in terms of toxicity and vulnerability to potentially lethal conditions such as infection and malignancy. Thus, there exists a need for a method of treating adult rheumatoid arthritis which does not entail the potentially lethal side effects associated with the treatments described above.

"Superantigens" have been considered as stimulants of the immune system in various autoimmune diseases including rheumatoid arthritis. Herman, A., et al. (1991) Annu. Rev. Immunol. 9:745-772; Drake, C.G. and Kotzin, B.L. (1992) J. Clin. Immunol. 12:149-162 (incorporated herein by reference). The gastrointestinal tract may be the site of immunologic stimulation by superantigens. There may be a defect in the ability of patients with adult rheumatoid arthritis to produce antibodies with the correct neutralizing specificities.

One approach to treating rheumatoid arthritis is to orally administer cow's milk to patients. See U.S. Patent No. 4,732,757 (Stolle, et al.). Stolle, et al. disclose that hyperimmunized milk containing a high titer of specific antibodies from animals actively and artificially immunized and boosted with large amounts of purified antigen is useful to treat rheumatoid arthritis. The drawbacks to this approach are several-fold. The cow donors pool must be specifically and actively immunized to a small subset of antigens. In addition, some patients have adverse reactions to consumption of bovine milk. Moreover, cow's milk does not contain the entire spectrum of antibodies present in a human. Furthermore, the effects of hyperimmune milk on inflammatory processes, such as rheumatoid arthritis, has largely been discarded. See Ormrod and Miller (1991) Agents and Actions, 32(3/4):160-166.

Another approach to the treatment of autoimmune diseases, of which rheumatoid arthritis is an example, is tolerization of the patient suffering from the autoimmune disease to the particular autoantigen(s) involved in the disease. In Weiner, et al., Science 259:1321-1324 (1993) (incorporated herein by reference), multiple sclerosis patients were orally administered bovine myelin protein, which contains two multiple sclerosis autoantigens. In Trentham, et al., Science 261:1727-1730 (1993) (incorporated herein by reference), rheumatoid arthritis patients were orally administered collagen, a presumed autoantigen. One drawback to tolerization is the identification of the correct autoantigen to which tolerance is to be induced.

In view of the unsuccessful and disadvantageous modalities currently employed there is a continued need to develop effective methods and compositions for the treatment of adult autoimmune rheumatoid arthritis.

SUMMARY OF THE INVENTION

The present invention is directed to a method for treating an adult rheumatoid arthritis patient by orally administering an amount of pooled human immunoglobulin in conjunction with an antacid which is sufficient to provide a clinically observable improvement in a patient's rheumatoid arthritic condition. The present invention is based on the discovery that the oral administration of pooled human immunoglobulin in conjunction with antacids, to patients with adult rheumatoid arthritis results in a significant clinical improvement in the rheumatoid arthritic condition of the patient. The present invention is also based on the discovery that there are no toxic effects of orally administered pooled human immunoglobulin in conjunction with an antacid to adult rheumatoid arthritis patients.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a Joint Tenderness and Swelling graph for patient GEC who was treated with oral gammaglobulin in combination with cimetidine.

Fig. 2 is a Joint Tenderness and Swelling graph for patent RR who was treated with oral gammaglobulin in combination with cimetidine.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention concerns a method for treating a patient with adult rheumatoid arthritis. This is accomplished by orally administering pooled human immunoglobulin in conjunction with an antacid. An immunoglobulin, introduced into the acidic environment of the human stomach, may suffer inactivation. To alleviate such inactivation and/or provide increased therapeutic efficacy, the pooled human immunoglobulin employed in the method of the present invention is administered in conjunction with an antacid. The present invention also contemplates pharmaceutical compositions comprising pooled human immunoglobulin and an antacid. While not wishing to be bound to a particular mechanism, the acid blocker may neutralize the otherwise acidic character of the gut thereby shielding the immunoglobulin from digestion in the stomach. Alternatively, the acid-blocker and immunoglobulin may synergistically provide remediation of arthritis symptoms by suppressing inflammatory mediators or immune-mediated inflammation.

Surprisingly, in accordance with the present invention it has now been discovered that encapsulated immunoglobulin IgG, intended to avoid the acidic character of the stomach and provide sustained release in the intestines, does not manifest any noticeable improvement relative to uncoated IgG. This determination demonstrates that the antacid is not merely shielding the immunoglobulin from the gut, but acting synergistically to improve the effectiveness of the immunoglobulin. Accordingly, the present invention contemplates pharmaceutical compositions containing pooled

immunoglobulin and an antacid which provides increased efficacy relative to pooled human immunoglobulin administered alone.

As used herein, the term "pooled human immunoglobulin" refers to an immunoglobulin composition containing polyclonal antibodies obtained from the plasma of thousands of human donors. The polyclonal antibodies may include IgG, IgA, IgM, etc. or fragments thereof. A preferred polyclonal antibody is IgG. A preferred immunoglobulin composition contains at least about 90% IgG polyclonal antibodies and trace amounts of other polyclonal antibodies such as, for example, IgA and IgM. Examples of pooled human immunoglobulin compositions useful in accordance with the present invention include, but are not limited to, Sandoglobulin®, Gammagard®, Gamimune® and Gammar®. In accordance with the present invention any pooled human immunoglobulin can be used.

"Antacid" when used herein denotes an H_2-blocker or acid blocker or other acid neutralizing agent which neutralizes and/or significantly reduces the acidic content of the gut. A preferred antacid useful in accordance with the teachings of the present invention is cimetidine.

A "clinically observable improvement" when used herein refers to a significant subjective remediation of symptoms associated with the patient's rheumatoid arthritic condition including, but not limited to, tender joint(s), swollen joint(s) and stiffness assessments. Significant subjective remediation of symptoms denotes a patient's self-assessment or a physician's assessment of stiffness, joint tenderness, swelling and the like. For example, an observable difference in swelling or

tenderness in even one arthritic joint is significant. Absence of swelling or tenderness in a previously affected joint is most significant.

Another aspect of the present invention provides a pharmaceutical composition comprising pooled human immunoglobulin, an antacid and a pharmaceutically acceptable carrier. In a preferred embodiment the composition comprises Sandoglobulin®, cimetidine and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredients, its use in the therapeutic compositions is contemplated.

"Treating" as used herein includes measures to ameliorate, suppress, mitigate or eliminate the clinical symptoms after the onset (i.e., clinical manifestation) of adult rheumatoid arthritis.

"Oral" administration as used herein includes oral, enteral or intragastric administration.

"In conjunction with" as used herein means before, substantially simultaneously with or after oral administration of antacid. Of course, the immunoglobulin composition can not precede or follow administration of an antacid by so long an interval of time that the relevant effects of the substance administered first have expired. Therefore, the immunoglobulin composition should usually be administered within a therapeutically effective time. By "therapeutically effective time," as

used herein, is meant a time frame in which the antacid or immunoglobulin is still active within the patient.

In a preferred embodiment, the pooled human immunoglobulin is produced by cold alcohol (e.g., ethanol) fractionation from the plasma of thousands of human volunteers.

In another preferred embodiment, pooled human immunoglobulin is purchased from Novartis Pharmaceuticals, where it is sold under the name Immune Globulin Intravenous (Human) Sandoglobulin®. Sandoglobulin® is a sterile, highly purified polyvalent antibody product containing, in concentrated form, all the IgG antibodies which regularly occur in the donor population. This immunoglobulin preparation is produced by cold alcohol fractionation from the plasma of over 16,000 volunteer donors. Sandoglobulin® (IGIV) is made suitable for intravenous use by treatment at acid pH in the presence of trace amounts of pepsin. The preparation contains at least 96% of IgG and with a neutral unbuffered diluent has a pH of 6.6 ± 0.2. Most of the immunoglobulins are monomeric (7 S) IgG; the remainder consists of dimeric IgG and a small amount of polymeric IgG, traces of IgA and IgM and immunoglobulin fragments [Römer J, Späth PJ: Molecular composition of immunoglobulin preparations and its relation to complement activation, in Nydegger UE (ed): Immunohemotherapy: A Guide to Immunoglobulin Prophylaxis and Therapy. London, Academic Press, 1981, p. 123.]. The distribution of the IgG subclasses corresponds to that of normal serum. Final container lyophilized units are prepared so as to contain 1, 3 or 6 g protein with 1.67 g sucrose and less than 20 mg NaCl per gram of

protein. The lyophilized preparation is devoid of any preservatives and may be reconstituted with sterile water.

In still another preferred embodiment, pooled human immunoglobulin is purchased from the Baxter Healthcare Corporation, where it is sold under the name Immune Globulin Intravenous (Human) Gammagard®. Gammagard® is a sterile, freeze dried preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. Gammagard® is manufactured by cold ethanol fractionation. Gammagard® contains at least about 90% IgG and trace amounts of IgA and IgM. Gammagard®, reconstituted to 5%, contains a physiological concentration of sodium chloride (approx. 8.5 mg/mL) and has a pH of 6.8 ± 0.4. The distribution of IgG subclasses is similar to that in normal plasma. Gammagard® is supplied lyophilized in 2.5, 5 or 10 g single use bottles. Each bottle of Gammagard® is furnished with a suitable volume of sterile water for reconstitution.

In yet another preferred embodiment, pooled human immunoglobulin is purchased from the Bayer Corporation, where it is sold under the name Gamimune®. Gamimune® is a sterile solution of highly purified human protein. Gamimune® contains 9-11% protein in 0.16-0.24 M glycine. At least about 90% of the protein is IgG monomer Gamimune® also contains traces of IgA and IgM. The distribution of IgG subclasses is similar to that found in normal human serum. Gamimune® like Gammagard® and Sandoglobulin® is made by cold ethanol fractionation of pools of human plasma obtained from thousands of volunteers.

In still another preferred embodiment, pooled human immunoglobulin is purchase from Centeon, L.L.C., where it is sold under the name Immune Globulin Intravenous (Human) Gammar®. Gammar® is a sterile solution of immunoglobulin, primarily immunoglobulin G (IgG), containing 16.5 ± 15% protein. Gammar® is prepared by cold alcohol fractionation of plasma pooled from at least 1000 donors. The pH of Gammar® is 6.8 ± 0.4. Gammar® also contains approximately 0.45% sodium chloride, thimerosal, at a concentration of 0.01% and 0.3M glycine. The above-described pooled human immunoglobulin preparations are merely exemplary of the class of pooled human immunoglobulin preparations useful in accordance with the present invention.

In order to enhance the effectiveness of the introduced immunoglobulin in the treated patient and provide a clinically observable improvement, an antacid is administered in conjunction with the pooled immunoglobulin. In a preferred embodiment the immunoglobulin composition and the antacid are administered simultaneously in a unitary pharmaceutical composition. In another preferred embodiment the immunoglobulin composition is administered at a therapeutically effective time after administration of the antacid. Preferably, the antacid is aluminum hydroxide or magnesium hydroxide such as Maalox®, Mylanta® or Tagamet® which are available commercially. Most preferably the antacid is an H2 blocker, such as Cimetidine or Ranitidine.

The dosage of antacid administered in conjunction with immunoglobulin depends on the particular H_2-blocker used. When the antacid is Mylanta®, between

15 ml and 30 ml is preferred. Most preferably the dosage of Mylanta® is 15 ml. When the cimetidine H2 blocker is used, the preferred dosage is between 400 and 800 mg per day.

The dosage of pooled human immunoglobulin administered to the patient may be varied dependent upon severity of the patient's arthritic condition and other clinical factors. Preferably, the dosage will be as small as possible while still providing a clinically observable result. The most preferable doses are those that have the largest effect in terms of alleviating the patient's arthritic condition. Dosages of the immunoglobulin composition may range from as little as 100 mg per day up to as much as 10 g per day. Dosages of 1000 mg of pooled human immunoglobulin per day have been found to result in significant improvement in the condition of patients with rheumatoid arthritis and cause little or no adverse side effects. Accordingly, 1000 mg per day is a preferred dose.

Although the chosen dose may be given in increments, it also may be given as a single dose. Further, although the dose of immunoglobulin may be administered at any time during the day, it is preferred that it be administered in the morning, prior to substantial patient activity.

The patient's arthritic condition can be determined, for example, by the patient's self-assessment of his or her pain, stiffness, etc. Another way to determine the patient's arthritic condition is for a physician to examine a patient's joint tenderness and swelling.

It is especially advantageous to formulate the pooled human immunoglobulin in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the rheumatoid arthritic subjects to be treated, each unit containing a predetermined quantity of pooled human immunoglobulin with or without an antacid calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifics for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the pooled human immunoglobulin, antacid and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a pooled human immunoglobulin for the treatment of adult rheumatoid arthritis herein disclosed in detail.

The pooled human immunoglobulin with or without an antacid is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the pooled human immunoglobulin in amounts ranging from about 100 mg to about 10 g and, if desired, an antacid in an amount ranging from about 400 to 800 mg.

Clinically observable results from the administration of immunoglobulin in conjunction with antacid may be observed in as little as 2 weeks. However, it may take up to 6 weeks to obtain measurable benefit. Initial dose levels used during the first few weeks of treatment may be reduced once clinical

improvement has been observed. Reductions in dose levels of up to 90% may be made after the first few weeks.

The oral treatment method in accordance with the present invention may be used to treat adult rheumatoid arthritis and other closely related autoimmune diseases such as spondyloarthopathies including but not limited to Ankylosing Spondylitis (AS), psoriatic arthritis, Reiter's Syndrome and the arthritis of inflammatory bowel disease including, but not limited to, ulcerative colitis and Crohn's disease. The treatment of spondyloarthopathies according to the present invention would employ the same dosages as for rheumatoid arthritis and the same treatment protocol.

Demonstrations of the treatment of patients in accordance with the present invention are set forth in the following non-limiting examples.

EXAMPLE 1

An open-label study was conducted to evaluate the safety of oral gammaglobulin. Five patients were selected who had severe, unremitting rheumatoid arthritis unresponsive to conventional therapy. The patients continued to receive their prescribed medical regimen, and in addition were given 1 gram of encapsulated (uncoated) gammaglobulin daily in a single dose for six weeks. There was no evidence of toxicity as a result of receiving oral gammaglobulin. Moreover, three of five patients showed improvement in the number of tender and swollen joints.

On the basis of the Phase I trial, a Phase II FDA approved double-blind placebo controlled trial was conducted in 28 patients with severe unresponsive rheumatoid arthritis to determine the efficacy of oral gammaglobulin in rheumatoid arthritis. Eight patients received 1 gram of uncoated gammaglobulin daily for 2 months, ten patients received 1 gram enteric coated gammaglobulin daily for 2 months, and 10 patients received a spite of optimum therapy with standard agents, including disease modifying anti-rheumatic drugs (DMARDs). Oral gammaglobulin was discontinued after 2 months, but the patients were followed for disease activity for an additional 2 months.

At the third month of observation 50% (4/8) of the patients treated with uncoated gammaglobulin fulfilled ACR criteria for 20% improvement compared to 11% of the placebo group (1/9) ($p<0.05$).

The entire group of 18 patients treated with gammaglobulin showed a significant reduction in the

number of swollen joints. The improvement was observed at every follow-up visit compared to the initial visit with an overall reduction of about 40% by the third and fourth months ($p<0.01$). In contrast, the placebo group did not show a significant reduction of swollen joints at any time in the course of the study compared to the initial examination. Furthermore, 5 of the patients with markedly reduced joint swelling treated with gammaglobulin showed at least 4-fold reductions in serum levels of C-reactive protein, rheumatoid factor, or both during the course of the study.

Patients in each study receiving 400 mg/day of the H_2 blocker, cimetidine were the best responders to oral gammaglobulin. There were no side affects attributable to taking oral gammaglobulin in this study. The results of this study indicated that oral administration of gammaglobulin in conjunction with an H_2 blocker were effective in the treatment of rheumatoid arthritis. The lack of toxicity indicated a favorable toxicity profile that made this treatment highly advantageous compared to other treatments or in combination with other treatments for rheumatoid arthritis.

The following is a description of patients who received both an H_2 blocker and oral immunoglobulin. These patients had the best clinical response. The patients improved more than 80%. Noticeably, the patients improved with respect to tender and swollen joints as well as physician's global assessment.

Patient #127, (CEG) a 75 year old Caucasian male with a history of sero-positive rheumatoid arthritis for 14 years. He was one patient in the placebo-

controlled double-blind study who took oral gammaglobulin in combination with cimetidine (400 mg/day). The patient was receiving a stable dose of cimetidine at the time the study was begun. This patient had clinically observable response. At the initial visit, he had 18 tender and 17 swollen joints. At the fourth visit, he had only 3 tender and swollen joints, or an improvement of 82%. The physician's initial global assessment was 8.0. At the fourth visit, the global assessment was 4.0. (Table I).

TABLE I

Patient ID: GEC Number 127

Month Number	Baseline	1	2	3	4
Number Tender Joints (Physician Assessment)	18		3	4	3
Number Swollen Joints (Physician Assessment)	17		10	10	3
Physician Total	35	ND	13	14	6

ND = not determined.

Patient No. 5, (RR) a 70 year old male with 12 year history of sero-positive rheumatoid arthritis with rheumatoid nodules. RR had severe uncontrolled disease almost exclusively involving his hands and wrists with erosions, deformities, and stiffness lasting all day. RR previously received gold therapy, but it was discontinued because of toxicity. RR was receiving methotrexate 15 mg/week, sulfasalazine 1 gm/day, Indocin® 25 mg at bedtime, Motrin® 1600 mg/day, Plaquenil® 400 mg/day, and Tagamet® 400 mg/day. Patient RR responded to oral immunoglobulin (given post-week 3) with clinically observable improvement, but flared two weeks after oral immunoglobulin was discontinued. (Table II).

TABLE II

Patient ID: R.R. Number 5

Week Number	0	1	2	3	4	5	6
A.M. Stiffness	all day	all day	all day	1	all day	4	0
Disability/Function	2	2	2	2	2	2	
Joint Tenderness (Number) (Patient Assessment)	12	6	8	7	6	4	4
Number Tender Joints (Physician Assessment)	19	3	9	6	4	1	2
Number Swollen Joints (Physician Assessment)	8	7	5	9	6	2	1
Physician Total	27	10	14	15	10	3	3

WHAT IS CLAIMED IS:

1. A method of treating adult autoimmune rheumatoid arthritis in a patient comprising orally administering to said patient an immunoglobulin composition comprising pooled human immunoglobulin in conjunction with a antacid in an amount sufficient to provide a clinically observable improvement in the rheumatoid arthritis of said patient.

2. The method of Claim 1 wherein said immunoglobulin composition comprises pooled human polyclonal IgG antibodies.

3. The method of Claim 2 wherein said immunoglobulin composition is selected from the group consisting of Sandoglobulin®, Gammagard® or Gamimune®.

4. The method of Claim 1 wherein said antacid is selected from the group consisting of aluminum hydroxide, magnesium hydroxide, cimetidine or ranitidine.

5. The method of Claim 1 wherein the amount of immunoglobulin composition which is administered to said patient is between 250 mg to 10 g per day.

6. The method of Claim 5 wherein the amount of immunoglobulin composition which is administered to said patient is about 1000 mg per day.

7. The method of Claim 1 wherein the amount of antacid which is administered to said patient is between 200 mg to 800 mg per day.

8. The method of Claim 7 wherein the amount of antacid which is administered to said patient is about 400 mg per day.

9. The method of Claim 1 wherein said immunoglobulin composition is administered in a unit dosage form.

10. The method of Claim 1 wherein said antacid is administered in a unit dosage form.

11. The method of Claim 1 wherein said immunoglobulin composition is in a powdered form.

12. The method of Claim 1 wherein said immunoglobulin composition is dispersed in pharmaceutically acceptable carrier.

13. The method of Claim 1 wherein said immunoglobulin composition and said antacid are administered simultaneously to said patient.

14. The method of Claim 1 wherein said immunoglobulin composition is administered at a therapeutically effective time after administration of said antacid.

15. A pharmaceutical composition comprising pooled human immunoglobulin, an antacid and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of Claim 15 wherein said pooled human immunoglobulin is Sandoglobulin®.

17. The pharmaceutical composition of Claim 15 wherein said antacid is cimetidine.

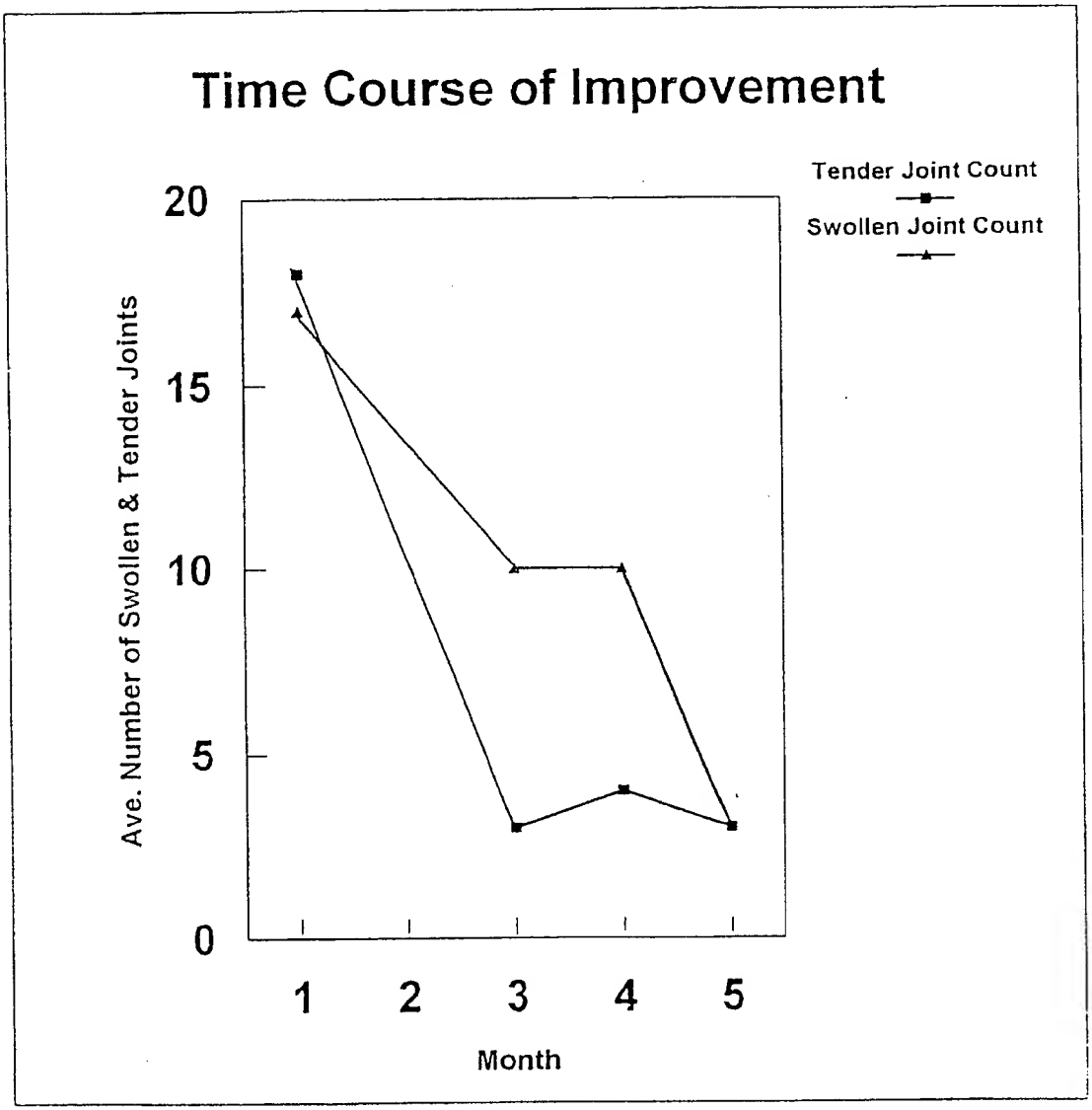
Time Course of Improvement
Tender Joint Count
Swollen Joint Count
Ave. Number of Swollen & Tender Joints
20
15
10
5
0
1
2
3
4
5
Month

FIGURE 1

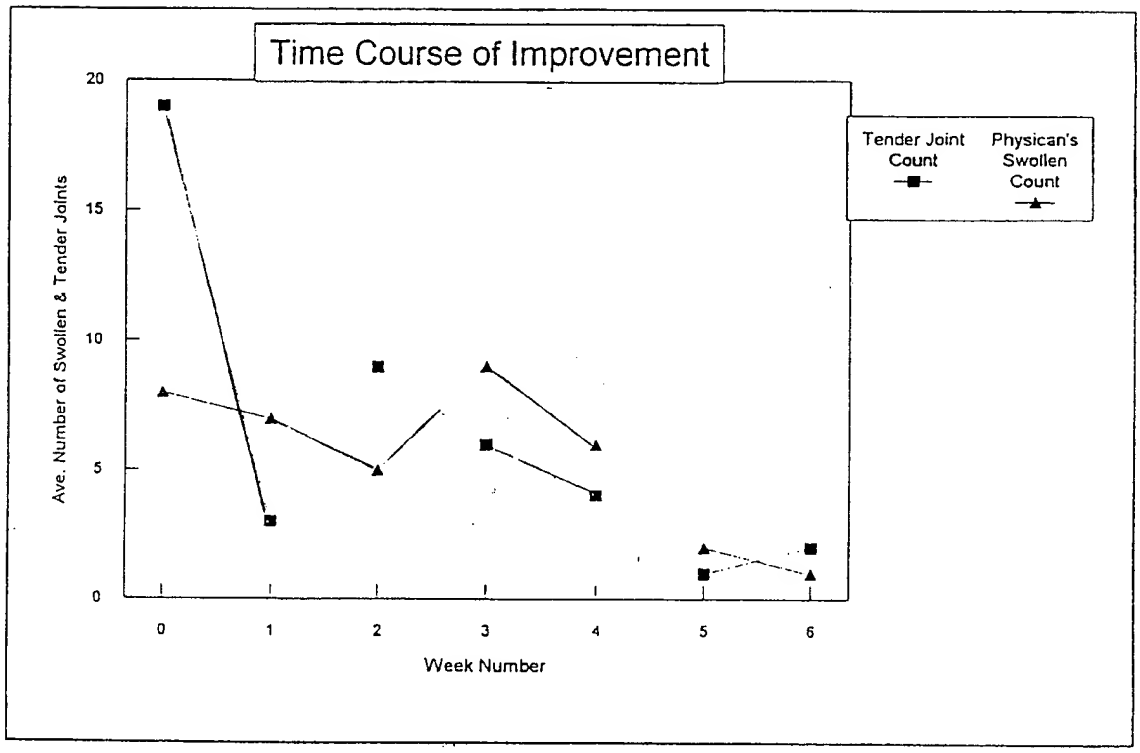
Time Course of Improvement
Ave. Number of Swollen & Tender Joints
20
15
10
5
0
0
1
2
3
4
5
6
Week Number
Tender Joint Count
Physican's Swollen Count

FIGURE 2

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 99/08578

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/395 //(A61K39/395,31:34,31:415,33:06,33:10)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 833 984 A (EIBL M ET AL) 10 November 1998 (1998-11-10) column 1, line 30 - line 35 column 4, line 25 - line 34 column 6, line 5 - line 7 column 6, line 46 - line 52 column 16, line 13 - line 17; claims 5,11	1,2, 4-15,17
Y	---	3,16
Y	GB 2 013 691 A (STOLLE RESEARCH AND DEVELOPMENT) 15 August 1979 (1979-08-15) claims 1-7	3,16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/08578

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 064 210 B (MILES LABORATORIES) 20 August 1986 (1986-08-20) column 2, line 51 - line 65 column 4, line 53 - line 59 column 6, line 59 -column 7, line 5; claims 1-4	15-17
A	GIANNINI E H ET AL: "Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis: a phase I/II study. Pediatric Rheumatology Collaborative Study Group 'see comments!." JOURNAL OF RHEUMATOLOGY, vol. 23, no. 5, May 1996 (1996-05), pages 919-24, XP000857451 abstract	1-17
A	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US AN97434949, 2 December 1997 (1997-12-02) PASHOV A ET AL: "A shift in encephalitogenic T cell cytokine pattern is associated with suppression of EAE by intravenous immunoglobulins (IVIg)." XP002124892 abstract & PASHOV A ET AL: "A shift in encephalitogenic T cell cytokine pattern is associated with suppression of EAE by intravenous immunoglobulins (IVIg)." MULTIPLE SCLEROSIS, vol. 3, no. 2, April 1997 (1997-04), pages 153-6,	1-17
A	MAKSYMOWYCH W P ET AL: "High dose intravenous immunoglobulin (IVIg) in severe refractory rheumatoid arthritis: no evidence for efficacy." CLINICAL AND EXPERIMENTAL RHEUMATOLOGY, vol. 14, no. 6, December 1996 (1996-12), pages 657-60, XP000857452 page 658, left-hand column, line 33 - line 35	1-17
A	FR 2 512 342 A (GLAXO GROUP) 11 March 1983 (1983-03-11) page 4, line 18 - line 21; claims 1-4	1-17

3

INTERNATIONAL SEARCH REPORT

..ernational application No.
PCT/US 99/08578

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/US 99/08578

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